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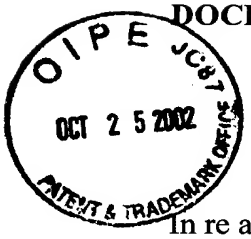


IN THE UNITED STATES PATENT AND TRADEMARK OFFICE



In re application of:

**Titievsky *et al.***

Serial No.: **09/410,319** Group Art Unit: **1655**

Filed: **October 1, 1999** Examiner: **A. Chakrabarti**

For: **A NOVEL RET-INDEPENDENT SIGNALING PATHWAY FOR GDNF**

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**DATE OF DEPOSIT: OCTOBER 25, 2002**

BOX AF
Assistant Commissioner for Patents
Washington, D.C. 20231

**AMENDMENT**

Dear Sir:

A Request for Continued Examination under 37 C.F.R. § 1.114 accompanies this Amendment. In response to the Official Action dated October 5, 2001, please amend the application, without prejudice, as follows.

*In the Claims*

Please cancel claims 92 to 115, without prejudice.

Please amend claims 1, 16, 83 and 87, without prejudice, to read as follows. A marked version to show changes made is enclosed.

1. (Twice amended) A method for identifying a compound that is an agonist of Ret-independent intracellular signaling effected by GPI-anchored receptors in nervous system cells comprising (i) incubating nervous system cells expressing GPI-anchored receptors, but not Ret, with a test compound and (ii) determining whether intracellular signaling has been effected in said cells, thereby identifying a compound that is an agonist of Ret-independent intracellular signaling effected by said GPI-anchored receptors.

16. (Twice amended) A method for identifying a compound that is an antagonist of Ret-independent intracellular signaling effected by GPI-anchored receptors in nervous system cells comprising (i) incubating nervous system cells expressing GPI-anchored receptors, but not Ret, with a test compound in the presence of a sufficient amount of an agonist of said Ret-independent intracellular signaling to effect intracellular signaling, and (ii) comparing the results

to controls not incubated with said compound, thereby identifying a compound that is an antagonist of Ret-independent intracellular signaling effected by GPI-anchored receptors.

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83. (Twice amended) A method for identifying a compound which is an agonist of Ret-independent intracellular signaling effected by GFRα receptors comprising (i) incubating lipid rafts prepared from cells having GFRα receptors with said compound and (ii) determining whether Src-type kinase is activated as compared to controls not incubated with said compound, thereby identifying a compound which is an agonist of Ret-independent intracellular signaling effected by GFRα receptors.

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87. (Twice amended) A method for identifying a compound which is an antagonist of Ret-independent intracellular signaling effected by GFRα receptors comprising (i) incubating lipid rafts prepared from cells having GFRα receptors with said compound in the presence of a sufficient amount of an agonist of the GFRα-dependent, Ret-independent intracellular signaling pathway to activate Src-type kinases and (ii) comparing the results to control experiments performed in the absence of said compound, thereby identifying a compound which is an antagonist of Ret-independent intracellular signaling effected by GFRα receptors.

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## REMARKS

Applicant respectfully requests entry of the present amendments, and reconsideration of the rejections set forth in the Office Action dated October 6, 2001, in view of the amendments and following remarks.

After entry of the amendment, Claims 1 to 91 will be pending in the application. No claims have been added. Claims 1, 16, 83 and 87 are amended herein to clarify that claimed methods are directed to identifying agonists and antagonists of ***Ret-independent intracellular signaling***. The amendment is supported throughout the application as originally filed, for example at page 3, lines 16 to 18. Claims 92 to 115, directed to non-elected subject matter, have been canceled, without prejudice. Applicants expressly reserve the right to pursue claims directed to such subject matter in one or more divisional applications.

***Response to Rejections***

Multiple rejections under 35 U.S.C. § 103 are pending in the application. Applicants respectfully disagree with the Examiner regarding these rejections for the reasons, for example, set forth in the response submitted September 24, 2001. In the interest of advancing prosecution of the application, however, Applicants have amended independent Claims 1, 16, 83 and 87 to more clearly define over the cited art. The specific pending rejections will be addressed in the discussion that follows.

Claims 1 to 6, 16 to 21, 30, 32, 39, 40 and 42 stand rejected under 35 U.S.C. § 103 over Ibanez *et al.* (WO 97/18240)("Ibanez") in view of Jefferies, U.S. Patent No. 5,981,194 ("Jefferies"), and further in view of Cacalano et al. (*Neuron* (1998) 21:53-62)("Cacalano").

As amended herein, independent Claim 1 defines a method for identifying a compound that is an agonist (and Claim 16, a method for identifying a compound that is an antagonist) of ***Ret-independent intracellular signaling***. Such methods are neither taught nor suggested in the cited art.

As properly recognized in the Office Action, Ibanez teaches methods for identifying GDNF analogs of c-Ret mediated intracellular signaling. There is absolutely nothing in Ibanez to suggest the existence of an alternative *Ret-independent* pathway for GDNF signaling.

This deficiency is not overcome by combining the teaching of Ibanez with either or both of the secondary references. The passages cited by the Examiner in Jefferies, at page 8, lines 31 to 48, and page 25, lines 38 to 58, describe methods for identifying modulators of p97 (a GPI-anchored protein), comprising incubating a cell expressing p97, and measuring the amount of iron uptake. However, the Examiner has failed to provide any reason why one investigating the mechanisms of GDNF intracellular signaling, the subject of Ibanez, would have any motivation to seek out or consider Jefferies. It appears that an attempt is made in the Office Action to provide a possible link between these two references, by virtue of the passage at column 10 of Jefferies, where it is stated that methods for treating Alzheimer's disease are presented.

However, these methods rely on the administration of p97, transferrin, transferrin receptors, or substances which are capable of reacting with same, and have nothing to do with GDNF, or GDNF signaling, as discussed in Ibanez. Thus, even if one of ordinary skill in the art to which Ibanez pertains were to read Jefferies, there is simply nothing in the combined teachings of these references that would lead such an artisan to conclude that GNDF signaling could be effected by a GPI-anchored receptor, independently of Ret.

Moreover, the lack of motivation to consult Jefferies is even more apparent when one considers the subject matter defined by independent Claim 30, for example, which is directed to methods for identifying a compound that is an agonist of GFRα1-dependent, Ret-independent signaling. Jefferies simply has nothing to do with GFRα1-dependent signaling.

Combination of Ibanez with Cacalano also fails to overcome the deficiencies of the primary reference. It is asserted in the Office Action that Cacalano teaches a method wherein GDNF is linked to GPI-anchored proteins, and wherein Ret(-/-) nervous system cells are used. It is respectfully asserted that this argument ignores the fact that Cacalano explicitly *teaches away* from the methods of the present invention, by expressly stating that GDNF signaling is effected by Ret. In this regard, Cacalano states:

> These findings substantiate the hypothesis that the receptors for the GDNF protein family are composed of two subunits: a GPI-linked ligand-binding protein that belongs to the GFRα family *and a signaling component that is represented by the transmembrane tyrosine kinase Ret* . . . .

> . . . Nevertheless, the severity of the phenotype of the *Ret*(-/-) mice, when compared with that of the *GFRα1*(-/-) mice, is consistent with the idea that *Ret is an essential, shared signaling component for the GDNF family of receptors*.

(*See* page 59, col. 1, paragraphs 2 and 6, emphasis added.) Thus, one of ordinary skill in the art, upon reading Ibanez and Cacalano, could only conclude that Ret is required for GDNF intracellular signaling. As stated above, this artisan would have no motivation to seek out Jefferies for any further insight in this regard, because Jefferies has nothing to do with GDNF signaling. Moreover, even if Jefferies were consulted, there is nothing in Jefferies to suggest that Ret-independent pathways for GDNF signaling exist, as discussed above.

From the foregoing, it is apparent that there is no motivation to combine these three references as has been done in the Office Action. Cacalano *teaches away* from the invention defined by Applicants' claims, and no motivation to seek out Jefferies has been provided. Moreover, it is respectfully submitted that even if the teachings of these three references are improperly combined, there is nothing that would lead one of skill in the art to the invention defined by Applicants' claims. Accordingly, Applicants respectfully request that the rejection of Claims 1 to 6, 16 to 21, 30, 32, 39, 40 and 42 over Ibanez, in view of Jefferies and Cacalano be withdrawn.

Claims 1 to 10, 15 to 24, 29 to 33, 38 to 40, 42, 43 and 48 to 58 stand rejected over the same references discussed above, further in view of Shen et al., (*J. Immunol.* (1994) 152:3017-3023)("Shen").

Shen is cited for methods of measuring intracellular signaling. However, as set forth above, the hypothetical combination of Ibanez, Jefferies and Cacalano fails to achieve the basic steps of Applicants' invention. Shen adds nothing to make up for the fundamental deficiency of failing to provide sufficient motivation to combine the references in a manner that could possibly achieve the claimed invention. Simply put, there is nothing additional in Shen that would lead one of skill in the art to understand that binding to a GPI-anchored receptors, such as GFRα1, could, in the absence of Ret, initiate intracellular signaling that would lead to activation of Src-type kinase, which could be measured as PLCγ activation, or an increase in intracellular $Ca^{2+}$ concentration. Thus, the combined teachings of Ibanez, Jefferies, Cacalano and Shen, to the extent that such combination is even proper, fails to teach or suggest the invention defined by Claims 1 to 10, 15 to 24, 29 to 33, 38 to 40, 42, 43 and 48 to 58. Accordingly, Applicants respectfully request that the rejection be withdrawn.

The Examiner has rejected claims 1-10, 12-13, 15-24, 26-27, 29-33, 35-36, 38-40, 42, 43, 45-46, 48-58, 68-70, 75-77, 79-85, 87-89, and 91 under 35 U.S.C. §103(a) over Ibanez in view of Jefferies, further in view of Cacalano, further in view of Shen, further in view of Dikic *et al.* (*Nature* (1996) 383:547-549).

Dikic is cited for a method of measuring intracellular signaling via a Src-type kinase by activation of MAPK. However, as set forth above, the hypothetical combination of Ibanez, Jefferies and Cacalano fails to achieve the basic steps of Applicants' invention. It is asserted that

Dikic teaches that Src-type kinase activation may be measured as activation of MAPK. However, Dikic contains nothing that would make up for the fundamental deficiencies of the other references discussed previously. Thus, the addition of this reference fails to render any of the pending claims obvious. Accordingly, Applicants request that this rejection be withdrawn, as well.

Claims 1-10, 12-24, 26-33, 35-40, 42, 43, 45-58, 68-71, and 75-91 stand rejected under 35 U.S.C. §103(a) over Ibanez in view of Jefferies, further in view of Cacalano, further in view of Shen, further in view of Dikic *et al.* (*Nature* (1996) 383:547-549), further in view of Finkbeiner *et al.* (*Neuron* (1997) 19:1031-1047).

Finkbeiner is cited for a method of measuring intracellular signaling via a Src-type kinase by activation of CREB. However, as set forth above, the hypothetical combination of Ibanez, Jefferies and Cacalano fails to achieve the basic steps of Applicants' invention. Shen, Dikic and Finkbeiner add nothing to make up for the fundamental deficiency of failing to provide sufficient motivation to combine the references in a manner that could possibly achieve the claimed invention. Accordingly, Applicants also request that this rejection be withdrawn.

The Examiner has rejected claims 1-91 under 35 U.S.C. §103(a) over Ibanez in view of Jefferies, further in view of Cacalano, further in view of Shen, further in view of Dikic *et al.* (*Nature* (1996) 383:547-549), further in view of Finkbeiner *et al.* (*Neuron* (1997) 19:1031-1047), further in view of Chalazonitis *et al.* (*Developmental Biol.* (1998) 204:385-406).

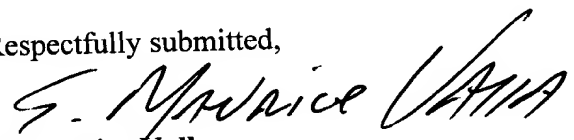
Chalazonitis is cited for the use of an anti-GFRα1 antibody. However, as set forth above, the hypothetical combination of Ibanez, Jefferies and Cacalano fails to achieve the basic steps of Applicants' invention. Shen, Dikic, Finkbeiner and Chalazonitis add nothing to make up for the fundamental deficiency of failing to provide sufficient motivation to combine the references in a manner that could possibly achieve the claimed invention. For this reason, Applicants respectfully request that the rejection be withdrawn.

## CONCLUSION

For the reasons discussed above, Applicant respectfully submits that the invention defined by Claims 1 to 91 is patentably distinct over the references cited by the Examiner. Accordingly, favorable reconsideration of the rejections under Section 103(a) and an allowance of these claims is respectfully requested.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned "**Version with markings to show changes made.**"

Respectfully submitted,



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Date: **October 25, 2002**

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